QSAR in Predictive Toxicology

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QSAR and Predictive Toxicology

QSAR is intended to focus attention and resources on chemicals most likely to have a specific behavior.

In predictive toxicology, QSAR provides the initial hypotheses before any testing is conducted

Proper integration with other alternative methods will:

- -eliminate testing of chemicals with low hazards
- -eliminate testing of chemicals similar to tested surrogates
- -identify potential hazards of a chemical most relevant to safety
- -integrate toxicology into virtual systems models

Quantitative Structure-Activity Relationship

- QSAR is an approach for understanding complex phenomena in chemical behavior
- There are simple rules to this approach
  - choose well-defined activity endpoints
  - choose plausible molecular descriptors
  - explore the data with statistics
  - test hypotheses with new data (ie. iterate)

  These rules are ignored in 90% of QSAR papers)

Initial EU Interpretation

- Select a defined endpoint
- Select available descriptors for modeling
- Gather training sets and create models
- Emphasis on validation of statistical models instead of mechanisms

Flaws in Initial Efforts

- Ignored the importance that QSAR models require two predictions:
  - predicting the intrinsic behavior (mechanism)
  - predicting the intensity factor (potency)
- QSAR models focused on endpoint-training data regardless of mechanisms
- QSAR models without clear logic for the domains are not accepted by regulators

What do we mean by Chemical Categories?

- A group of chemicals that have some features that are common
  - Structurally similar e.g. common substructure
  - Property e.g. similar physicochemical, topological, geometrical, or surface properties
  - Behaviour e.g. (eco)toxicological response underpinned by a common Mechanism of Action
  - Functionality e.g. preservatives, flavourings, detergents, fragrances

Annex IX of REACH

Substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or "category" of substances.

Application of the group concept requires that physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for a reference substance within the group by interpolation to other substances in the group (read-across approach). This avoids the need to test every substance for every endpoint.

OECD Definition of Category

- A chemical category is a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity
- These structural similarities may create a predictable pattern in any or all of the following parameters: physicochemical properties, environmental fate and environmental effects, and human health effects

OECD Manual for Investigation of High Production Volume (HPV) Chemicals.

The Chemical Category Solution

- Forming chemical categories shifted emphasis to intrinsic chemical activity
- Entire categories of chemicals can be assessed when only a few are tested
- Filling data gaps involves read-across & trend analysis, not just QSAR models
- Enables defensible hazard assessment with elaborate QSAR models